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EXAMINER	
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ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@crbcp.com

Office Action Summary	Application No.	Applicant(s)
	10/571,744	PARTHASARADHI REDDY ET AL.
	Examiner	Art Unit
	TAMTHOM TRUONG	1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,10-16,18,21-25,27 and 30-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7, 10-16, 18, 21-25, 27 and 30-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5-5-11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

Applicant's amendment of 5-5-11 has been fully considered. Regarding claims 16 and 24, applicant's argument has not been found persuasive for the rejections of 112/2nd paragraph, items (a) and (b), and thus, said rejections remain outstanding. Regarding claims 7, 18 and 27, their dependency has been corrected, and thus, the rejections of 112/2nd paragraph, items (c), (d) and (e) are withdrawn.

Claim 7 is now dependent on the pending claim 4.

Claim 18 is now dependent on the pending claim 14.

Claim 27 is now dependent on the pending claim 23.

Judging from the Final Action of 9-3-09, and the (RCE) Non-Final Action of 11-8-10, claims 4, 14, 23, and 34 were **not** previously presented with specific ketonic solvents or specific alcoholic solvents. Had said claims been amended with specific ketonic and alcoholic solvents, the 102 rejection would not have been made by Examiner Truong. Therefore, it is taken that said claims are **now** amended (*not* previously amended) with specific ketonic or alcoholic solvents.

Thus, the 102 and 103 rejections are **revised as necessitated by amendment**.

Claims 6, 8, 9, 17, 19, 20, 26, 28 and 29 are cancelled.

Claims 1-5, 7, 10-16, 18, 21-25, 27 and 30-61 are pending.

The rejection of 102(b) is maintained for claims 1-3. The rejection of 103 is revised to include presently amended claims 4, 14, 23, and 34 and claims dependent thereon.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 16, 25, 34-46 and 51-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 16 and 25 recite the phrase "anti-solvent" which has indefinite metes and bounds despite applicant's citation of a definition from US Patent No. 4,668,768, and the instant specification, paragraphs [0011] and [0015] describing the "anti-solvent" as a solvent for initiating or forcing "crystallization of a solute from a solution." A search in EAST yields several US patents using the term "anti-solvent" for various processes of crystallization or polymerization. In US **7,927,613**, the "anti-solvent" is used in a process of "crystallization from a melt". In US **7,872,153**, the "anti-solvent" is used for a **salt** to get precipitated out as it has poor solubility. In US **7,923,026**, the "anti-solvent" is used in a process to make a "hydrosol". Last but not least, in US **4,354,921**, the "anti-solvent" is used to separate wax from a dewax oil-solvent solution. Depending on the solubility of a compound, the "anti-solvent" is **not** the same for all crystallization processes. Sometimes an "anti-solvent" is a ketonic solvent (e.g., all those recited in the instant claim 4), but sometimes it is an aromatic solvent (e.g., benzene, toluene, etc.), or a water-miscible solvent (e.g., alcohols such as all those recited in claim 4), or an alkane (e.g., hexane, or heptane), and others such as: ethyl acetate, acetonitrile, ethers, etc. In the

instant case, the specification does not define or cite an example of "anti-solvent". Thus, it is unclear for one skilled in the art to determine what an appropriate "anti-solvent" would be. Furthermore, an "anti-solvent" is used in crystallizing a **salt**, *not* a free base. The working Examples 3, 4 and 5 did not use a second solvent besides the first ketonic or alcoholic solvent to form a suspension with the alfuzosin free base. However, it was used in said examples. Thus, it is unclear if the scope of "anti-solvent" includes heat.

b. Claim 34 and claims dependent thereon recite the limitation of '***activated tetrahydro-2-furoic acid***' which there is no definition or description of an "activated" tetrahydro-2-furoic acid. In the specification, paragraph [0020] only describes the '*activated tetrahydro-2-furoic acid*' as "tetrahydro-2-furoic acid having its carboxylic acid group in a conventional activated form". Applicants quoted an excerpt from WO 2004/022629 describing carboxylic acid groups in activated form that has a different function in **polymer**. In the instant case, the *tetrahydro-2-furoic acid* is a starting material in which applicants want the carboxylic acid in the activated form, but do not cite examples of such a form. The working Examples 1 and 2 only use *tetrahydro-2-furoic acid*, not its activated form. Thus, it is unclear what the activated form of tetrahydro-2-furoic acid is, and when it is used.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-3 remain rejected under 35 U.S.C. 102(b) as being inherently anticipated by **Manoury** (US 4,315,007). The alfuzosin free base is produced in Example I, in the step where the *N_1-Methyl-N_2-tetrahydrofuroylpropylemediamine* reacted with *4-amino-2-chloro-6,7-dimethoxyquinazoline* to form a precipitate which got filtered off. See the following excerpt:

distilled. N_1-Methyl-N_2-tetrahydrofuroylpropylenediamine, which boils at 114°–116° C. under a pressure of 0.07 mm Hg, is collected.

The IR spectrum shows the disappearance of the band due to the —C≡N radical.

A suspension of 3.7 g (0.02 mol) of the above amine and 4.8 g (0.02 mol) of 4-amino-2-chloro-6,7-dimethoxyquinazoline in 35 ml of isoamyl alcohol is then heated to the reflux temperature. The mixture is kept at the boil for 7 hours and left to stand overnight and the precipitate is then filtered off and washed with ethyl acetate and then with ether.

Note, although claims 1-3 recite "Crystalline alfuzosin base", the working examples 3-5 did not indicate a crystalline form of alfuzosin free base as said examples simply stated a "solid" form with no melting point given.

Thus, it is inherent that the claimed crystalline form of alfuzosin base is the same as the "precipitate" of alfuzosin base in Example I of US'007.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-5, 7, 10-16, 18, 21-25, 27 and 30-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Manoury** (US'007) in view of Wikipedia (reference for Methyl isobutyl ketone and Alcohol). In Example I, Manoury described the process of making the alfuzosin base by reacting *N_1-Methyl-N_2-tetrahydrofuroylpropylemediamine* **with** *4-amino-2-chloro-6,7-dimethoxyquinazoline*. The alfuzosin base got precipitated out, and washed with **ethyl acetate**, a solvent that has similar polarity with methyl isobutyl ketone used in the process recited in the instant claims 4, 5, 7, 10-16, 18, 21-22.

Note, the claimed processes do not reflect what described in the working examples 3-5 of the instant specification. The claim language gave the impression that the alfuzosin base was a solid that formed a suspension with a ketonic or an alcoholic solvent. When, in fact, in said examples, the alfuzosin base was an **oil residue**, that mixed with a solvent, which turned into a "**clear solution**" upon heating. Thus, the claimed process only differs from Manoury's Example I by the choice of solvent. In Example I of US'007, the two starting materials formed a suspension in **isoamyl alcohol** (which is **iso-pentanol**) which is a **water miscible** solvent like methanol, ethanol, or t-butyl alcohol as recited in the above claims. The suspension was heated, and left standing overnight to form a **precipitate** (solid alfuzosin base), which got

washed with ethyl acetate, a solvent that has similar polarity with methyl isobutyl ketone for use as an "anti-solvent".

4. The process recited in claims 23-25, 27, and 30-33 requires the acid addition salt of alfuzosin reacting with a base to "liberate alfuzosin base", and then crystallizing the alfuzosin base from a ketonic or alcoholic solvent. Said process can be found in the fourth step of Manoury's Example II, see the following excerpt:

On repeated recrystallization from 2-propanol one obtains 3 g of N_1-(4-amino-6,7-dimethoxyquinazol-2-yl)-N_1-methylpropylenediamine hydrochloride melting at about 270° C.

A solution of 0.987 (0.0085 mol.) of tetrahydrofuroic acid and 1.37 g (0.0085 mol) of carbonyldiimidazole in 30 ml. of tetrahydrofuran is stirred for 10 minutes at 20° C., then heated at 40° C. for 30 minutes until no more carbon dioxide is liberated. Then one adds 2.2 g (0.0075) of the foregoing diemine and heats under reflux for 90 minutes. The solvent is evaporated and one adds 2-N sodium hydroxide to the residue. After stirring the aqueous layer is decanted. The residual oil is taken up in chloroform, the organic solution is washed with 2-N

Note, when the tetrahydrofuroic acid **reacted** with the N_1-(4-amino-6,7-dimethoxyquinazol-2-yl)-N_1-methylproplylenediamine hydrochloride (**also known as the forgoing diemine**), the HCl salt of the alfuzosin was obtained, which got converted into an alfuzosin base by the addition of a base (i.e., sodium hydroxide). This alfuzosin base (a residual oil) was taken up in chloroform as opposed to a ketonic or alcoholic solvent. However, chloroform has low solubility in water **just as the methyl isobutyl ketone**, which is useful in a liquid-liquid extraction that allows the oil of alfuzosin base to be separated from the sodium hydroxide.

From the working examples 3-5 in the specification, it appears that the ketonic or alcoholic solvent was used like an "anti-solvent" to free the alfuzosin base from the organic solvent used during the reaction of the quinazoline-diamine with the tetrahydrofuroic acid. Thus, from the teaching of Manoury, it would have been obvious to select a solvent such as a ketonic or alcoholic solvent because said solvents would have been expected to be an effective "anti-solvent" for separating the solid alfuzosin free base.

5. Claims 34-61 recite a process that requires starting materials as mentioned in the 4th paragraph of Example II of US'007, and the resulting alfuzosin was in the HCl salt form which got converted into a free base by the addtion of **sodium hydroxide.** The free base of alfuzosin got liberated as a residual oil, and could be converted into a solid by the addition of isoamyl alcohol as described in Example I of the same reference. The choice of solvent is within the level of one skilled in art since said solvent is apparently used as an "anti-solvent". Therefore, at the time of the invention, it would have been obvious to develop a process of making a solid alfuzosin base by the details disclosed in Examples I and II of Manoury.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAMTHOM TRUONG whose telephone number is (571)272-0676. The examiner can normally be reached on Monday thru Friday (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Tamthom N. Truong
Examiner
Art Unit 1624

/JAMES O. WILSON/
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6-16-11